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UNIVERSITÉ DE SHERBROOKE

Dynamique laryngée lors de la ventilation nasale chez l'agneau nouveau-né

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Liste des abréviations

CRF = Capacité rédiduelle foncitonnelle

CT = Cricothyroïdien

Dia = Diaphragme

EV = Éveil

EMG = Électromyogramme

PS = Pression de support

PTVAS = Pression à travers les voies aériennes supérieures

SA = Sommeil agité

SC = Sommeil calme

TA = Thyroaryténoïdien

VC = Volume contrôlé

VPPIn = Ventilation à pression positive intermittente par voie nasale

Résumé

Mise en contexte : Contrairement à la ventilation endotrachéale, la ventilation à pression positive intermittente par voie nasale (VPPIn) doit faire progresser la colonne d'air à travers les voies aériennes supérieures. Alors que des études endoscopiques chez l'humain adulte suggèrent qu'une fermeture de la glotte peut limiter la ventilation alvéolaire en VPPIn, aucune donnée analysant le comportement des muscles laryngés n'est encore publiée. De plus, la dynamique laryngée en VPPIn n'a pas encore été étudiée chez les nouveau-nés.

But du projet : Le but de ce travail est donc de décrire la réponse des muscles laryngés à la VPPIn chez l'agneau nouveau-né sans sédation et leur impact sur la ventilation pulmonaire.

Méthodes : À cette fin, neuf agneaux nouveau-nés ont été instrumentés pour étudier les stades de conscience, l'activité électromyographique (EMG) d'un muscle constricteur (thyroaryténoïdien, TA) et dilatateur (cricothyroïdien, CT) de la glotte, l'EMG du diaphragme (Dia) ainsi que pour mesurer les pressions au niveau de la trachée et du masque. La ventilation nasale était délivrée via un masque nasal en mode volume contrôlé (VC) et pression de support (PS).

Résultats : Nos résultats démontrent qu'une augmentation du niveau de VPPIn en éveil et en sommeil calme entraîne à l'inspiration une disparition progressive de l'EMG du Dia et du CT et l'apparition de l'EMG du TA ainsi qu'une

augmentation de la pression à travers les voies aériennes supérieures (PTVAS). Cette dernière est plus marquée en mode VC que PS. De plus, l'augmentation de l'activité du muscle TA est associée à une limitation de la ventilation pulmonaire. Moins fréquemment, la transmission des pressions à travers les voies aériennes est totalement bloquée par une fermeture active et complète de la glotte. Ce dernier phénomène se retrouve habituellement en sommeil agité, caractérisé par de fréquentes et irrégulières bouffées d'EMG du TA.

Conclusion : La VPPIn s'accompagne d'une fermeture glottique active chez l'agneau nouveau-né non sédationné, particulièrement en mode VC, causant une augmentation de la résistance glottique. Ces observations suggèrent que les cordes vocales peuvent limiter activement la ventilation pulmonaire en VPPIn chez les nouveau-nés humains.

Mots clés : muscle thyroaryténoïdien, muscle cricothyroïdien, période néonatale, stades de conscience, ventilation à pression positive intermittente.

Introduction

La ventilation à pression positive intermittente par voie nasale (VPPIn) est maintenant couramment utilisée en période néonatale (GOLDBART et GOZAL, 2004). Des études ont démontré son efficacité pour traiter le syndrome de détresse respiratoire (KIEFFER et al., 1997), l'apnée du prématuré (BARRINGTON et al., 2001, LEMYRE et al., 2002), et pour accélérer le sevrage de la ventilation par tube endotrachéal (DAVIS et al., 2001, KHALAF et al., 2001). De précédentes études utilisant une visualisation glottique directe par endoscopie chez des humains adultes ont démontré une fermeture laryngée lors de la VPPIn, particulièrement en mode volume contrôlé (VC) (JOUNIEAUX et al., 1995[1], JOUNIEAUX et al., 1995[2], PARREIRA et al., 1996a, PARREIRA et al., 1996b, PARREIRA et al., 1997). Cette fermeture des cordes vocales augmente progressivement avec l'augmentation du support ventilatoire plus important et entraîne une diminution de la ventilation alvéolaire (RODENSTEIN, 2001). La publication d'épisodes de diminution de la saturation artérielle en oxygène lors de la VPPIn chez des humains adultes endormis souligne l'intérêt clinique d'élucider les mécanismes physiologiques entourant cette fermeture glottique (DELGUSTE et al., 1991). En période néonatale, une telle fermeture glottique pourrait entraîner une fuite de la colonne d'air vers l'œsophage et ainsi causer des distensions gastro-intestinales et des perforations gastriques (GARLAND et al., 1985).

Bien que la fermeture glottique observée endoscopiquement en VPPIn suggère un mécanisme actif par la contraction des muscles adducteurs des cordes vocales (constricteurs glottiques), aucune étude n'a encore analysé l'activité

électromyographique (EMG) des muscles intrinsèques du larynx lors de ce type de ventilation. Finalement, aucune donnée n'est disponible sur la dynamique laryngée lors de la VPPIn en période néonatale.

Le laboratoire de recherche respiratoire néonatale a donc entrepris d'élucider les différents impacts physiologiques de la ventilation nasale en période néonatale. Le but de l'étude était de tester les deux hypothèses suivantes : 1) Que la fermeture glottique observée chez l'agneau en VPPIn est aussi présente en période néonatale; 2) Que cette fermeture glottique est causée par une augmentation de l'activité EMG du muscle thyroaryténoïdien (TA, un constricteur de la glotte) et une diminution de l'activité EMG du muscle cricothyroïdien (CT, un dilatateur glottique). Les expériences de cette étude ont été conduites en mode volume contrôlé (VC) et pression de support (PS) lors des différents stades de conscience. Le modèle expérimental et les données obtenues lors de cette étude permettront au laboratoire de poursuive les recherche sur les mécanismes centraux entraînant les changements de la dynamique laryngée observés.

Article

LARYNGEAL RESPONSE TO NASAL VENTILATION IN NON-SEDATED NEWBORN LAMBS

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ABSTRACT

Although endoscopic studies in adult humans have suggested that laryngeal closure can limit alveolar ventilation during nasal intermittent positive ventilation (nIPPV), there are no available data regarding glottal muscle activity during nIPPV. In addition, laryngeal behavior during nIPPV has not been investigated in neonates. The aim of the present study was to assess laryngeal muscle response to nIPPV in non-sedated newborn lambs. Nine newborn lambs were instrumented for recording states of alertness, electrical activity (EMG) of glottal constrictor (thyroarytenoid, TA) and dilator (cricothyroid, CT) muscles, EMG of the diaphragm (Dia), and mask and tracheal pressures. Nasal intermittent positive ventilation in pressure support (PS) and volume control (VC) modes was delivered to the lambs *via* a nasal mask. Results show that increasing nIPPV during wakefulness and quiet sleep led to a progressive disappearance of Dia and CT EMG and to the appearance and subsequent increase in TA EMG during inspiration, together with an increase in trans-upper airway pressure (TUAP). On rare occasions, transmission of nIPPV through the glottis was prevented by complete, active glottal closure, a phenomenon more frequent during active sleep epochs, when irregular bursts of TA EMG were observed. In conclusion, results of the present study suggest that active glottal closure develops with nIPPV in non-sedated lambs, especially in the VC mode. Our observations further suggest that such closure can limit lung ventilation when raising nIPPV in neonates.

Keywords: thyroarytenoid muscle, cricothyroid muscle, diaphragm, states of alertness, intermittent positive-pressure ventilation.

INTRODUCTION

Nasal intermittent positive pressure ventilation (nIPPV) is increasingly used in the neonatal period (12) as treatment for respiratory distress syndrome (22), apneas of prematurity (3, 27) and as a bridge between endotracheal tube ventilation and spontaneous ventilation (6, 19). Previous studies using endoscopic observations in adult humans have shown that laryngeal closure can occur during nIPPV, especially in the volume control (VC) mode (17, 18, 34-36). In addition, laryngeal closure appears to increase with increasing ventilatory support, together with decreasing sub-glottal (alveolar) ventilation (40). Such laryngeal behavior is of high clinical importance since it has been linked to falls in oxygen saturation when increasing nIPPV during sleep in adult humans (7), and could divert positive pressure from the airways, leading to increased gastric distension (11). However, although the glottal closure observed endoscopically during nIPPV suggests an active contraction of glottal constrictor muscles, there are, to our knowledge, no data on glottal muscle EMG during nIPPV. Moreover, there are no currently available studies on laryngeal dynamics during nIPPV in the neonatal period. Thus, the aim of the present study was to test the hypotheses that 1) glottal narrowing during nIPPV is also present in the neonatal period, especially in the VC mode; 2) glottal narrowing during nIPPV is due to both an increase in thyroarytenoid (TA, a glottal constrictor) and a decrease in cricothyroid (CT, a glottal dilator) muscle electrical activity (EMG). The experiments were conducted in the VC and pressure support (PS) modes throughout the different states of alertness.

MATERIALS AND METHODS

Experiments were conducted in 9 mixed-bred term lambs aged from 3 to 5 days and weighing 4.2 kg (standard deviation SD 1.2; range 3.1 to 7) on the day of the experiment. All lambs were born at term by spontaneous vaginal delivery and housed with their mother in our animal quarters. The study protocol was approved by the ethics committee of the Université de Sherbrooke for animal care and experimentation.

Surgical preparation

Surgery was performed 1-3 days after birth under general anaesthesia (1 - 2% Isoflurane + 30 - 50% N_2O + 48 – 68% O_2). Intramuscular atropine sulphate (0.1 mg/kg) and ketamine (10 mg/kg) were injected prior to endotracheal intubation. Vital sign monitoring included electrocardiogram, rectal temperature, pulsed oximetry, end tidal CO_2, venous pH and glycemia. A mixture of dextrose 5%, NaCl 3 mEq/kg/day, KCl 1.5 mEq/kg/day and Ca^{2+} 2 mEq/kg/day was systematically infused per-operatively. Bipolar enamelled chrome wire electrodes were inserted into the thyroarytenoid (TA, a glottal constrictor), cricothyroid (CT, a glottal dilator) and diaphragm (Dia) muscles for recording electromyographic (EMG) activity (20). Custom-designed electrodes for electro-encephalogram (EEG), electrooculogram (EOG) and ECG recordings were also implanted as previously described (39). A custom catheter was inserted between the third and fourth tracheal rings to record sub-glottal pressure (26). Leads from each electrode were subcutaneously tunnelled to exit on the back of the lambs. Finally, an

arterial catheter (Insyte, 18GA, Infusion Therapy Systems, Sandy, UT) was inserted into a radial artery for blood sampling and gas analysis.

Post-operative care included daily intramuscular injection of penicillin G (Duplocillin 0.05 ml/kg/day) and gentamicin (5 mg/kg/day) until the end of the experimentation. The arterial catheter was flushed daily with heparin solution. Lambs were euthanized at the end of experiments by pentobarbital overdose. Correct electrode positioning was systematically verified at autopsy.

Experimental equipment

Ventilatory equipment. Nasal ventilation was performed with a Siemens Servo 300 ventilator and Servo Screen (Siemens Corporation, New York, NY) with heated (33°C) and humidified air. A custom-made nasal mask was built from a plaster shell filled with dental paste to fit the muzzle of each lamb as previously described (42). Briefly, the mask included a double nasal canula, a naso-gastric tube and a plastic catheter for end tidal CO_2 ($P_{ET}CO_2$) sampling.

Recording Equipment. Polysomnographic recordings were obtained by using our custom-designed radiotelemetry system with channels for EEG, electrooculogram (EOG), electrocardiogram (ECG) and 4 EMGs, as previously described (28, 29). The raw EMG signals were sampled at 500Hz, rectified and moving-time averaged on 100 ms. Mask pressure (a measure of the level of ventilatory support) and sub-glottal pressure (a measure of the ventilatory support reaching the lower airways) were recorded using two calibrated pressure transducers (MP 45-30-871, Validyne, Northridge, CA). Thoracic and abdominal volume variations were qualitatively assessed with their sum using respiratory inductance plethysmography (Respitrace, NIMS, Miami

Beach, FL). Arterial hemoglobin O_2 saturation (S_pO_2) was monitored with a probe attached at the base of the tail (38). $P_{ET}CO_2$ was continuously recorded using a CO_2 analyzer (Capnomac II, Datex-Ohmeda Canada Inc., Mississauga, ON, Canada), with a 50 ml/min flow sampling rate. Arterial blood gases and pH were also measured (IL 1306; Instrumentation Laboratory, Lexington, MA) and corrected for rectal temperature of the lamb (1). All signals were recorded on a Power Macintosh 7300 using the Acknowledge 3.2 acquisition software (Biopac Systems, Santa Barbara, CA).

Design of the study

The study was performed without sedation and at least 48 hours after surgery. The lambs were comfortably positioned in a sling with loose restraints. The study was designed to allow for simultaneous recording of EEG, EOG, ECG and EMG activity, variations of sub-glottal and mask pressure, respiratory movements, $P_{ET}CO_2$ and SpO_2 while using different levels of ventilation in the three different states of alertness. Arterial blood gases (PaO_2, $PaCO_2$, pHa) were measured at each level of ventilation.

Following a first recording with the nasal mask only (no CPAP, *i.e.,* no connection to the ventilator), ventilatory support was initiated *via* the nasal mask at CPAP 4 cmH_20. Two ventilatory modes, i.e. pressure support (PS) and volume control (VC), were used in all lambs in a random order. In the PS mode, three different levels of positive inspiratory pressure (PIP) were studied, namely 10, 15 and 20 cmH_20, while maintaining positive end expiratory pressure (PEEP) at 4 cmH_2O, as used in a previous study in adult humans (34, 36). The trigger was adjusted in flow mode at the lowest (easiest) stable setting. In the VC mode, respiratory rate (RR) and tidal volume (V_T) were initially set at the same level as when the lamb was spontaneously breathing with CPAP 4 cmH_2O (VC

baseline). Minute ventilation was then successively increased three times (VC #1, VC #2 and VC #3). Following preliminary tests, VC#1 was associated with an increase in RR to 40 or 50 breaths per minute (mean 42, SD 4.2, range 40 to 50) to avoid both auto-PEEP and rebreathing. VC#2 and VC#3 corresponded to an increase in V_T with 15 or 20 ml increments (depending on the lamb's weight) to a maximum of 23 ml/kg (SD 3.2, range 18 to 27). Positive end expiratory pressure was maintained at 4 cmH_2O throughout the VC mode experiments. Since stable ventilation has been shown to be difficult to obtain in the pressure control mode in a previous study (36) and during our preliminary tests in lambs, this mode was not tested in the present study. Every effort was made to obtain recordings in wakefulness (W), quiet sleep (QS) and active sleep (AS) at each level of ventilation. At any given time during experiments, ventilation was stopped if the following criteria were met: 1) lamb discomfort or agitation; 2) obvious abdominal distension or presence of liquid reflux *via* the nasogastric tube; 3) sub-glottal pressure over 30 cmH_2O; 4) presence of auto-PEEP; 5) inability to obtain the three states of alertness after one hour of continuous recording.

Data analysis

States of alertness. Standard electrophysiological and behavioural criteria were used to define W, QS and AS, from EEG, EOG and continuous observation (39). Arousal from QS was characterized by sudden disappearance of high-amplitude, low-frequency waves on the EEG trace, together with sudden appearance of any EMG activity and increase in heart rate, whereas arousal from AS was recognized by direct observation of the lamb and disappearance of intense EOG activity.

Respiratory parameters. For each state of alertness and every ventilatory level, an observer blinded to the goal and hypothesis of the study selected 20 consecutive breaths, which had to be preceded and followed by 20 seconds of stable respiratory pattern. Thereafter, respiratory parameters (inspiratory moving time average amplitude of CT, TA and Dia EMG, RR, mask and sub-glottal pressures and $P_{ET}CO_2$) were quantified, analyzed and averaged on the 20 selected breaths, using the Acknowledge (Version 3.7.0, Biopac Systems, Santa Barbara, CA) and Microsoft Excel software. In the present study, the qualifier "inspiratory" was used for Dia, CT and TA muscle EMG activities during nIPPV, when they occurred simultaneously with lung inflations, even when there was no evidence of central inspiratory drive *i.e.,* no visible Dia EMG activity. For both Dia and CT muscles, the inspiratory EMG maximal amplitude measured during W with no CPAP was averaged and used as reference value (100%) for subsequent calculations in the different ventilatory modes and states of alertness in each lamb. Since no TA EMG was recorded during inspiration in spontaneous, baseline breathing, the averaged EMG maximal amplitude recorded during 5 swallows was chosen as the reference value (100%). In addition, the pressure difference between mask and sub-glottal pressures, *i.e.,* the trans-upper airway pressure (TUAP), was calculated and analyzed on the same 20 breaths during baseline breathing. Analysis of the relationship between TUAP and TA EMG was conducted in each lamb as follows. Both TA EMG and TUAP were measured at 2 discrete time points during each lung inflation in the VC mode, at the highest level of ventilation (VC#3), when TA EMG was present. As airflow, by definition, is constant in the VC mode, any increase in TUAP indicated an increase in trans-upper airway resistance. Finally, one additional lamb was further instrumented with a chronic catheter positioned just above the glottis to directly measure transglottal

pressure (TGP) (10). The latter parameter, together with measurement of airflow (Hewlett-Packard 21070-60040 pneumotachograph interposed between the ventilator and nasal mask) enabled us to study the relationship between trans-glottal resistance (TGR) ($TGR = \frac{TGP}{Airflow}$) and TA EMG in VC#3.

Statistical analysis. Statistical analyses were performed using the SAS software version 9.1 (SAS Institute Inc., Cary, IL). Results were first averaged in each lamb, then in all lambs as a whole, and expressed as mean and standard deviation (SD). Normality was first tested using the Shapiro-Wilks test. Blood gases, which assumed a normal distribution, were analyzed using ANOVA with repeated measures. All the other analyses (CT, TA and Dia EMG, TUAP and respiratory rate) were performed using the Poisson regression model with repeated measures (GENMOD procedure). Power analysis was performed for each variable using the Nquery 4.0 software. Unless specified, all non-statistically significant results given in this report have been tested beforehand for at least 80% power. Finally, regression analysis (REG and MIXED procedures) were also performed for testing the relationship between trans-upper airway pressure and TA EMG in the VC#3 mode. All results with p value < 0.05 were considered as statistically significant.

RESULTS

Of the nine lambs that underwent surgery, CT and TA muscles could be analyzed in 8 lambs only, due to displacement of the electrodes observed at autopsy in one lamb. Total duration of polysomnographic recordings analyzed was 2151 min, with a mean recording time of 239 min (SD 60; range 149 to 369). Mean duration of states of alertness in each lamb was 187 min (SD 63; range 103 to 330) in W, 47 min (SD 20; range 18 to 74) in QS and 4 min (SD 5; range 0 to 13) in AS.

Baseline breathing with no CPAP in wakefulness

Regular phasic inspiratory Dia and CT EMG were consistently observed in all lambs during baseline recording with no CPAP, *i.e.,* with the nasal mask in place but without the ventilator. In addition, phasic CT EMG was observed during the second part of expiration (E_2) in 4 out of 8 lambs, while consistently absent in the first part of expiration (E_1 or post-inspiratory period). No tonic CT EMG was present during baseline breathing with no CPAP. While phasic expiratory TA EMG was observed in E_1 in 4 out of the 8 lambs studied, TA EMG was consistently absent during both inspiration and E_2 in all lambs. Values for the various respiratory parameters measured during baseline breathing and during different ventilatory support modes are given in table 1.

Breathing with CPAP 4 during wakefulness

A small but statistically significant decrease in RR was observed with CPAP 4, as compared to no CPAP ($p < 0.0001$). No changes in inspiratory Dia EMG was observed

from breathing with no CPAP to CPAP 4 ($p = 0.32$). In contrast, a significant decrease in inspiratory CT EMG was observed from no CPAP to CPAP 4 ($p = 0.03$). Inspiratory CT EMG even disappeared in two of the 8 lambs when breathing with CPAP 4. Small amplitude, phasic inspiratory TA EMG was observed in one of the 8 lambs with CPAP 4. A significant decrease in expiratory TA EMG was observed with CPAP 4, as compared to no CPAP ($p = 0.03$). Finally, a small but significant increase in inspiratory TUAP was observed from CPAP 0 to CPAP 4 ($p < 0.0001$) (table 1).

Pressure support mode in wakefulness

A progressive decrease in RR was observed with each step increase in ventilatory support. Overall, a 58% decrease in respiratory rate was observed with PS 20/4 as compared to no CPAP ($p < 0.0001$). A progressive decrease in Dia EMG was observed with increasing PS, dropping to half of the values recorded with no CPAP ($p < 0.0001$). Similarly, inspiratory CT EMG decreased steadily with every increase in PS and eventually disappeared in 5 lambs ($p < 0.0001$). Phasic inspiratory TA EMG appeared with PS 10/4 (in one lamb) and was eventually observed in 7 of the 8 lambs with PS 20/4 ($p < 0.0001$) (see figure 1 as an example of EMG changes between no CPAP and PS 20/4). Meanwhile, expiratory (E_1) TA EMG decreased and disappeared, except in 3 lambs where both inspiratory and expiratory (E_1) TA EMG were present. Finally, a significant increase in TUAP was observed from CPAP 0 to PS 20/4 ($p = 0.01$) (see table 1 and figure 2 for graphic illustration).

Volume control mode in wakefulness

While RR was maintained virtually constant in the VC mode throughout the experiment, V_T was progressively increased from 56 ml in VC baseline to 89 ml in VC #3. As noted previously in PS mode, both Dia ($p = 0.0004$) and CT ($p < 0.0001$) EMG decreased from no CPAP and from VC baseline to VC #3. Also, inspiratory TA EMG appeared in 7 out of 8 lambs and increased progressively from VC baseline to VC #3 ($p = 0.006$). Expiratory (E_1) TA EMG was still present in 4 lambs in VC #3 (3 of which already had E_1 TA EMG activity with no CPAP). A major increase in TUAP was progressively observed with increasing VC, culminating at 17.5 cmH_2O on average in VC #3 ($p < 0.0001$) (see table 1). Interestingly, the pattern of inspiratory TA EMG was different in VC, when compared to PS. Indeed, the slope of the increase in TA at the onset of inspiration was less abrupt in VC than in PS. Also, during PS mode, following the early peak of activity at onset of lung inflation, a decrescendo in inspiratory TA EMG was observed, as opposed to a more sudden decrease in VC mode (figure 3).

Further analysis showed that the increase in trans-upper airway pressure was significantly correlated with TA EMG in VC #3 in each lamb, indicating that trans-upper airway resistance increased simultaneously with TA EMG ($p < 0.001$) in the VC mode in each lamb (figure 4A).

End tidal CO_2 and arterial blood gases

A slight but statistically significant decrease in PCO_2 and $P_{ET}CO_2$ was observed when increasing nasal ventilation in both PS and VC (table 2). While averaged values remained within normal physiological ranges, PCO_2 was outside the normal range in some lambs. One hypercapnic lamb during no CPAP (PCO_2 = 50 Torr) decreased its

PCO_2 to 45 Torr in VC#3. Two other lambs went from normocapnia to PCO_2 = 32 Torr. A fourth lamb remained hypercapnic throughout the entire experiments (maximal PCO_2 = 49 Torr). However, neither TA nor CT EMG evolved differently in lambs with PCO_2 values out of the normal range.

Apneas

Twenty-nine central apneas were recorded during the experiments (0.8 apnea/h), with a mean duration of 8.7 sec (SD 2.9; range 3 to 14.9). Most apneas occurred in W (25/29) in the PS mode (15/29) and were preceded by a sigh (24/29). Seven apneas occurred during no CPAP, five during CPAP 4 and finally two in VC mode. No episodes of periodic breathing were observed in any of the lambs or ventilatory modes.

Influence of the states of alertness

Overall, the majority of results obtained in PS and VC modes in QS were identical to those obtained in W, including a significant decrease in inspiratory Dia and CT EMG and a significant increase in both inspiratory TA EMG and TUAP (see table 3). However, low statistical power precluded any possible comparison of glottal muscle EMG response between QS and W for the same level of nIPPV in a given ventilatory mode.

No statistical analysis could be performed in AS, due to a lack of sufficient data, including 4 out of 9 lambs, who did not sleep in AS. Semi-quantitative observations suggested that Dia EMG was increased in CPAP 4, PS and especially in the VC mode. In addition, while CT EMG was clearly increased in both inspiration and expiration in all five lambs in AS, TA EMG did not appear to change, aside from bursts of TA EMG resembling bursts of non-nutritive swallows. Interestingly, the latter occasionally

occurred simultaneously with ventilator insufflations, leading to a total glottal blockade of ventilation, with a marked increase in trans-glottal pressure and an absence of inspiratory volume variation on the respiratory plethysmography in VC mode (see figure 5). Complete glottal closure in such cases induced a marked elevation in mask pressure in the VC mode, from 15 to 20 cmH_2O in normal breaths to as high as 55 cmH_2O. The VC mode was also associated with asynchronism between respiration and the ventilator in 5 out of 8 AS episodes in the VC mode, due to irregular respiratory pattern of the lambs in AS.

DISCUSSION

The present results in lambs indicate that raising nIPPV progressively inhibits phasic laryngeal dilator EMG and triggers the onset of phasic laryngeal constrictor EMG during lung inflations in wakefulness and quiet sleep. In addition, our observations further suggest that modifications in laryngeal muscle EMG are responsible for active glottal narrowing, which limits lung inflation during nIPPV. The observation that nIPPV is accompanied by modifications of laryngeal muscle activity is a unique finding and furthers previous endoscopic reports of glottal narrowing in adult humans. We believe that such findings are of high physiological interest, and may bear significant consequences for neonatal respiratory care.

Inspiratory glottal muscle electrical activity during nIPPV

Thyroarytenoid muscle inspiratory activity. When present, phasic respiratory contraction of the TA muscle normally occurs in early expiration (13, 23, 31, 32, 41, 47). This has been shown to be especially important in the neonatal period as a braking mechanism for expiratory lung emptying, ultimately helping the newborn to maintain a sufficiently high residual functional capacity, thus preventing atelectasis and enhancing oxygenation (4, 8, 13). Conversely, phasic inspiratory TA EMG is rare with eupneic breathing (37) and has been observed only in limited experimental or pathological conditions such as anoxic gasping (15, 30, 46), hypoxia (9), C fiber stimulation by capsaicin (31), upper airway occlusion (21) or in patients with amyotrophic lateral

sclerosis (16). Consequences and mechanisms of phasic inspiratory TA EMG in the above conditions are unclear.

To our knowledge, the activation of TA EMG with lung inflation during nIPPV is a unique observation, whose causal mechanisms are likely related to stimulation of extra- and/or intrathoracic airway receptors by increased transmural pressure. Accordingly, the earlier onset of TA EMG during lung inflation in the PS *vs.* the VC mode (see figures 1 and 3) may be related to the fact that airway pressure peaks earlier in the PS mode. As recently reviewed (2), available but scarce data suggest that, while stimulation of slow adapting receptors inhibits TA EMG (5, 13), stimulation of rapidly adapting receptors or C fibers could enhance phasic TA EMG, although in the expiration phase (14, 45). Alternatively, increased afferent activity from positive pressure receptors in the upper airways (pharynx and/or larynx) (33, 43) could be involved in the activation of inspiratory TA EMG, as suggested by recent results from experiments on isolated larynx in piglets (44). Involvement of other laryngeal receptors such as "flow" (thermal) receptors (43, 44) during nIPPV is less likely, since insufflated air utilized in the present study was heated and humidified. Finally, while passive hyperventilation to hypocapnia using nIPPV has been shown to activate TA EMG during expiration (24), involvement of this mechanism would at best be marginal. Indeed, even if PCO_2 was slightly decreased in a few lambs, the increase in TA EMG was similar in lambs with or without any change in PCO_2.

Cricothyroid muscle inspiratory activity. As recently shown in both humans and lambs, CT muscle acts as a glottal dilator in phase with the posterior cricoarytenoid muscle during inspiration (25, 32, 41). The present results showing disappearance of inspiratory CT EMG in newborn lambs in both PS and VC modes extend similar

observations in adult humans during nIPPV in the PS mode (24). Disappearance of phasic inspiratory Dia and CT EMG is likely, or at least partly, related to the increase in vagal afferent activity from bronchopulmonary stretch receptors (2). Reflexes originating from the upper airways can also be at play, secondary to loss of negative inspiratory pressure. Indeed, this negative inspiratory pressure normally increases posterior cricoarytenoid muscle activity in eupneic breathing (44). Finally, while passive hypocapnia reduces inspiratory CT EMG (24), this mechanism is most likely not involved in the present study, as explained previously for TA EMG.

Active inspiratory glottal narrowing during nIPPV

The present observations of both enhanced TA and decreased CT EMG during lung inflations strongly suggest that the glottis is actively narrowed in inspiration during nIPPV, as previously hypothesized from endoscopic observations during nIPPV in the VC mode in adult humans (40). The simultaneous increase in TA EMG and trans-upper airway pressure (TUAP) observed in all lambs at constant airflow in the VC mode indicates that upper airway resistance is increased with TA EMG during lung inflation. This increase in upper airway resistance could theoretically be related to active contraction of pharyngeal constrictor muscles, *e.g.*, at the velopharyngeal level, or to passive mechanisms such as narrowing of the pliable laryngeal inlet due to the Venturi effect. However, several evidences strongly suggest that active glottal closure is at least partly responsible for the increase in upper airway resistance. Firstly, this study provides one example in which that trans-glottal resistance increases with TA EMG during inflation in the VC mode (see figure 4B). Secondly, previous endoscopic observations in adult humans have shown that the glottis narrows in inspiration during nIPPV in the VC

mode (17, 18). Finally, the existence of a complete stoppage in pressure transmission throughout the upper airways during the burst in TA EMG activity in AS, as shown in figure 5, strongly suggests an active mechanism.

Increased laryngeal resistance during lung inflation in nIPPV may consequently limit lung ventilation with increasing levels of nIPPV, especially in the VC mode. This is readily apparent in the one lamb illustrated in figure 4B during wakefulness, with lower tidal volume when both TA EMG and trans-glottal pressures are higher. In addition, bursts of TA EMG during AS were at times strong enough to totally prevent transmission of ventilator insufflations to the trachea (Figure 5). Though such bursts of TA EMG have already been reported in adult humans during eupnea (23) and in newborn lambs during nIPPV (42), their relation with effective ventilation has not previously been discussed. Furthermore, such limitation of pressure transmission across the glottis may further increase the risk of gastric dilation and digestive perforations in newborns (11).

While we were not able to compare the PS and VC mode with regards to glottal resistance during lung inflations, some observations are nonetheless noteworthy. Indeed, as previously described, TA EMG in PS mode in all lambs was maximal in early inspiration and progressively decreased to zero before the end of inspiration (see figure 1), allowing prolonged transmission of constant ventilator pressure through the open glottis. Conversely, TA EMG in VC mode increased in parallel with ventilator pressure throughout inspiration, which suggests that glottal resistance was maximal when ventilator pressure peaked at the end of inspiration. In addition, pressure transmission across the glottis was further impeded in VC mode by a much shorter inspiratory duration, comparatively to the PS mode (see figure 3). While these observations could explain the important differences in TUAP between the PS and VC modes (2.3 and 17.5

cm H_2O respectively, see table 1), it is clear that a definitive assessment regarding the superiority of one nIPPV mode *vs.* the other in achieving lung ventilation in the newborn cannot conclusively be reached from the present results.

In conclusion, the present study shows that nIPPV, in either the PS or VC mode, induces both an inspiratory increase in glottal constrictor EMG and a decrease in glottal dilator EMG in lambs. Presence of this active glottal narrowing significantly limits lung ventilation, especially in the VC mode.

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TABLES

Table 1: Respiratory parameters during no CPAP, CPAP 4 cmH_2O and nasal intermittent positive pressure ventilation in wakefulness

	CT inspi EMG	TA inspi EMG	Dia inspi EMG	Inspi TUAP (cm H_20)	RR (breaths / min)
No CPAP	1	0	1	-0.2 (0.5; -1.1-+0.6) [b,c,e]	40 (11;24-56) [b,c,d,e]
CPAP 4	0.58 (0.44; 0.18-1.54) [a,d,e]	0	0.9 (0.2; 0.7-1.3) [c,d,e]	1.1 (0.4; 0.5-1.7) [e]	35 (8;25-44) [d,e]
PS 10 /4	0.34 (0.23; 0.11-0.78) [a,d,e]	0.07 (0.05; 0.03-0.20) [a,d,e]	0.7 (0.3; 0.3-1.1) [a,d,e]	1.1 (1.0; 0.1-3.1) [e]	34 (8;25-45) [d,e]
PS 15 /4	0.27 (0.18; 0.12-0.68) [a]	0.14 (0.09; 0.06-0.34) [a,b,e]	0.4 (0.2; 0.2-0.7) [a,e]	1.5 (2.5; 0.0-8.1)	25 (9;14-37) [e]
PS 20 /4	0.25 (0.09; 0.17-0.46) [a]	0.29 (0.17; 0.06-0.53) [a,b]	0.5(0.2; 0.3-0.7) [a]	2.3 (1.6; 0.2-5.4)	17 (6;9-26)
VC base	0.59 (0.45; 0.10-1.40) [a,g,h,i]	0.10 (0.08; 0.03-0.24) [i]	0.8 (0.3; 0.4-1.3) [g,h,i]	3.9 (2.4; 1.4-9.7) [a,h,i]	40 (8;30-53)
VC # 1	0.38 (0.41; 0.11-1.22) [a,h,i]	0.17(0.16; 0.04-0.45) [a]	0.4 (0.2; 0.2-0.7) [a]	6.7 (4.8; 2.6-18.1) [a,h,i]	41 (2;40-45)
VC # 2	0.18 (0.10; 0.08-0.37) [a]	0.20 (0.14; 0.04-0.44) [a]	0.4 (0.1; 0.1-0.6) [a]	10.4 (2.6; 6.7-14.3) [a,i]	41 (3; 40-50)
VC # 3	0.21 (0.08; 0.08-0.35) [a]	0.26 (0.17; 0.05-0.53) [a]	0.5 (0.3; 0.1-1.2) [a]	17.5 (5.5; 10.6-25-8) [a]	40 (5;30-50)

RR : respiratory rate; Dia, CT, TA inspi EMG : diaphragm, cricothyroid, thyroarytenoid phasic inspiratory electrical activity; TUAP : trans upper airway pressure; CPAP : continuous positive airway pressure; PS : pressure support; VC : volume control ventilation.
All superscript letters are $P < 0.05$: [a] *vs.* no CPAP ; [b] *vs.* CPAP4 ; [c] *vs.* PS 10 / 4 ; [d] *vs.* PS 15 /4 ; [e] *vs.* PS 20 / 4 ; [f] *vs.* VC base ; [g] *vs.* VC # 1 ; [h] *vs.* VC # 2 ; [i] *vs.* VC # 3.

Table 2: Arterial blood gases (pH, PCO_2, PO_2 and HCO_3^-) and $P_{ET}CO_2$ (%) relative to each ventilatory mode

	pHa	$PaCO_2$	PaO_2	HCO_3^-	$P_{ET}CO_2$
No CPAP	7.37 ± 0.04 [a,b,c]	42 ± 5 [b,c,e,f]	90 ± 19	24 ± 4	5.5 ± 1.1 [a]
CPAP 4	7.37 ± 0.04	42 ± 5	95 ± 17	24 ± 4 [h]	5.6 ± 1.0 [l,j]
PS 10 / 4	7.37 ± 0.05 [d]	41 ± 5	94 ± 17	24 ± 5	5.5 ± 1.0 [k]
PS 15 /4	7.38 ± 0.05	41 ± 5	90 ± 13	24 ± 5	5.6 ± 0.9 [l,m]
PS 20 / 4	7.37 ± 0.06	40 ± 6	94 ± 13	23 ± 6	5.4 ± 1.2
VC base	7.38 ± 0.06	40 ± 6	93 ± 13	24 ± 4	5.3 ± 0.6 °
VC # 1	7.38 ± 0.06	41 ± 4	95 ± 15 [g]	24 ± 4	5.4 ± 0.7
VC # 2	7.39 ± 0.06	40 ± 5	94 ± 15	24 ± 5	5.1 ± 0.8
VC # 3	7.37 ± 0.05	39 ± 5	100 ± 15	22 ± 5	5.3 ± 0.8

Values are expressed as mean ± SD. All superscript letters are $p < 0.05$: [a] CPAP 0 *vs.* VC # 1 ; [b] CPAP 0 *vs* VC # 2 ; [c] CPAP 0 *vs* VC # 3 ; [d] PS 10 /4 *vs* VC # 2 ; [e] CPAP 0 *vs* VC base ; [f] CPAP 0 *vs* PS 20 /4 ; [g] VC # 1 *vs* VC # 2 ; [h] CPAP 4 *vs* PS 20 /4 ; [l] CPAP 4 *vs* VC # 1 ; [j] CPAP 4 *vs* VC # 2 ; [k] PS 10 / 4 *vs* VC # 1 ; [l] PS 15 / 4 *vs* VC # 1 ; [m] PS 15 / 4 *vs* VC # 2 ; ° VC base *vs* VC # 2

Table 3: Respiratory parameters during no CPAP, CPAP 4 cm H_2O and nasal intermittent positive pressure ventilation in quiet sleep

	CT inspi EMG	TA inspi EMG	Dia inspi EMG	Inspi TUAP (cm H_20)	RR (breaths / min)
No CPAP	0.85 (0.18;0.66-1.07) [b,c,d,e]	0 [e]	1.1 (0.2;0.8-1.5) [b,c,d,e]	-0.7 (1.2; -2.5-+0.6) [b,c,d,e]	42 (9;29-53) [b,c,d,e]
CPAP 4	0.41 (0.27;0.16-0.92) [c,d,e]	0 [d,e]	0.8 (0.2;0.6-1.2) [c,d,e]	1.1 (0.6;0.4-2.3) [c]	35 (10;24-51) [d,e]
PS 10 /4	0.26 (0.25; 0.10-0.85)	0.07 (0.06;0.02-0.22) [e]	0.6 (0.2;0.3-.09)	0.7 (0.7;0.1-2.4)	33 (9;24-47) [d,e]
PS 15 /4	0.22 (0.08;0.11-0.36)	0.13 (0.08;0.05-0.29)	0.5 (0.3;0.1-1.1)	0.8 (0.7:0.0-2.5) [e]	25 (8;13-37) [e]
PS 20 /4	0.21 (0.13;0.04-0.35)	0.20 (0.19;0.02-0.48)	0.4 (0.3;0.1-0.7)	1.8 (1.3;0.7-4.2)	16 (4;10-21)
VC base	0.52 (0.50;0.11-1.35) [h,i]	0.08 (0.06;0.03-0.20) [i]	0.9 (0.5;0.3-1.7) [g,h,i]	3.3 (1.1;1.9-5.1) [a,g,h,i]	40 (9;31-54)
VC # 1	0.39 (0.57;0.09-1.67)	0.13 (0.10;0.04-0.31) [i]	0.4 (0.1;0.3-0.7) [a,i]	6.7 (3.9;2.7-14.4) [a,h,i]	40 (1;38-40)
VC # 2	0.21 (0.08;0.09-0.28) [a,i]	0.10 (0.02;0.09-0.13) [i]	0.3 (0.2;0.1-0.5) [a]	9.8 (1.9;7.7-11.9) [a,i]	40 (0;40)
VC # 3	0.18 (0.06;0.09-0.21) [a]	0.29 (0.17;0.17-0.48) [a]	0.3 (0.1;0.1-0.4) [a]	17.6 (4.4;13.4-23.6) [a]	38 (5;30-40)

RR : respiratory rate; Dia, CT, TA inspi EMG : diaphragm, cricothyroid, thyroarytenoid phasic inspiratory electrical activity; TUAP : trans upper airway pressure; CPAP : continuous positive airway pressure; PS : pressure support; VC : volume control ventilation. Note that the statistical power is < 80% for Dia, CT and TA inspi EMG in VC baseline and VC #3.
All superscript letters are $P < 0.05$: [a] *vs.* no CPAP ; [b] *vs.* CPAP4 ; [c] *vs.* PS 10 / 4 ; [d] *vs.* PS 15 /4 ; [e] *vs.* PS 20 / 4 ; [f] *vs.* VC base ; [g] *vs.* VC # 1 ; [h] *vs.* VC # 2 ; [I] *vs.* VC # 3.

FIGURE LEGENDS :

Figure 1: Electrical activities of thyroarytenoid, cricothyroid and diaphragm muscles during nasal intermittent positive pressure ventilation (left: no CPAP; right: pressure support 10 / 4) during wakefulness. Nasal ventilation inhibits diaphragm and CT EMG and triggers inspiratory TA EMG, which limits sub-glottal (tracheal) pressure until late inspiration. Abbreviations: TA: thyroarythenoid muscle EMG; ∫TA: moving time averaged TA; CT: cricothyroid muscle EMG; ∫CT: moving time averaged CT; Dia: diaphragm muscle EMG; ∫Dia: moving time averaged Dia; Pulmonary volumes: sum signal of the respiratory inductance plethysmograph (inspiratory upwards). Inspiration (i) and expiration (e) are delimited according to lung inflation duration.

Figure 2: Variations in inspiratory cricothyroid (CT, left), thyroarytenoid (TA, center) and diaphragm (Dia, right) EMG from baseline breathing to nasal intermittent positive pressure ventilation in the pressure support (top diagrams, A) and volume control (bottom diagrams, B) modes. The x axis represents varying levels of ventilation while the y axis represents the % of variation from baseline activity (CT and Dia) or % of maximal activity during swallowing (TA) as defined in data analysis.

Figure 3: Differences in respiratory parameters between pressure support (left) and volume control modes (right) during wakefulness. Note: 1) the sudden increase in TA EMG in pressure support compared to a progressive increase in volume control mode; 2) the disappearance of TA EMG in late inspiration in pressure support compared to

continuous TA EMG throughout inspiration in volume control mode; 3) the sub-glottal pressure plateau in late inspiration in pressure support, which is not observed in volume control mode. See figure 1 for abbreviations.

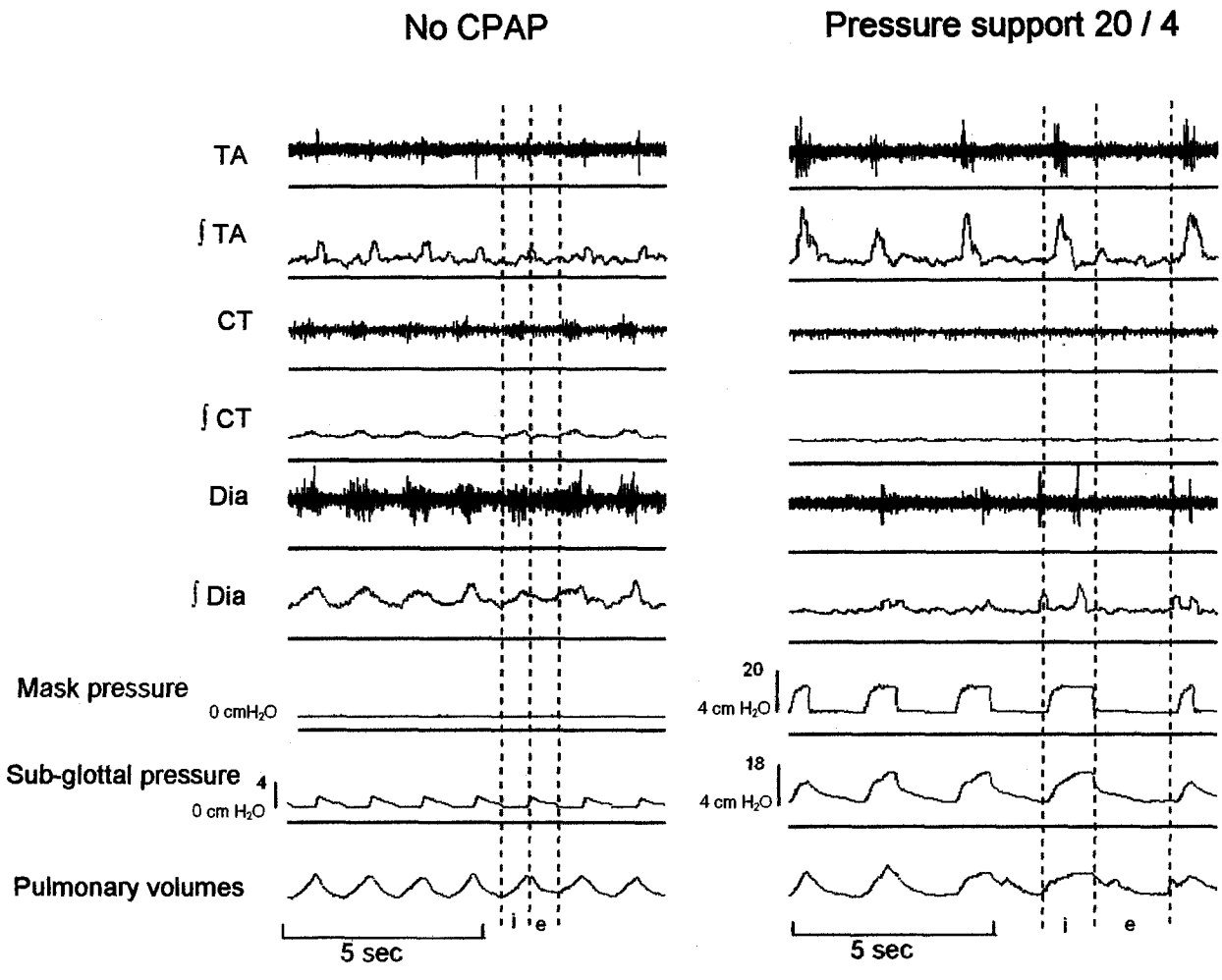
Figure 4: Increase in upper airway resistance during nIPPV in the volume control mode. Figure 4A depicts the relationship between trans-upper airway pressure (TUAP, cm H_2O) and thyroarytenoid muscle electrical activity (TA EMG, arbitrary units) in seven lambs during nIPPV in the volume control mode (VC#3) during wakefulness. Note that the bottom left graph has a different y axis scale. The middle lower graph represents the 95% confidence interval equation (σ_x and σ_{int} : SD of the slope and intercept with x axis), for the six upper lambs (the last lamb being excluded because of significant differences from the other lambs). The increase in TUAP with TA EMG at constant airflow (VC#3) indicates that upper airway resistance increases when TA EMG increases, suggesting that an active glottal closure occurs in response to pulmonary inflations. See text for further explanation.

Figure 4B : The above hypothesis is further supported by the significant relationship between trans-glottal resistance (TGR), and TA EMG in one lamb during nIPPV in the volume control mode during wakefulness (upper graph). Lower right graph shows increase in trans-glottal pressure (TGP, cm H_20) during peak TA EMG activity (asterisks) with constant airflow ($l \cdot s^{-1}$). Dashed lines delimit the inspiratory (i) and expiratory (e) phases of the respiratory cycle. See figure 1 for other abbreviations.

Figure 5: Complete laryngeal closure during bursts of TA EMG (asterisks) with no transmission of the ventilator strokes (mask pressure, black arrowheads) to the lungs

(sub-glottal pressure, white arrows) in the volume control mode in active sleep (right column). Indeed, with TA inspiratory EMG activity, maximal mask pressure increased from 17 to 32 cmH_2O and sub-glottal pressure dropped from 12 to 7 cmH_2O. High amplitude, tonic cricothyroid EMG activity was usually present in active sleep in the 5 lambs studied in this particular state. The left traces were obtained during wakefulness in the volume control mode in the same lamb.

Figure 1


No CPAP
Pressure support 20 / 4
TA
∫ TA
CT
∫ CT
Dia
∫ Dia
Mask pressure
0 cmH2O
Sub-glottal pressure
4
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18
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Figure 2

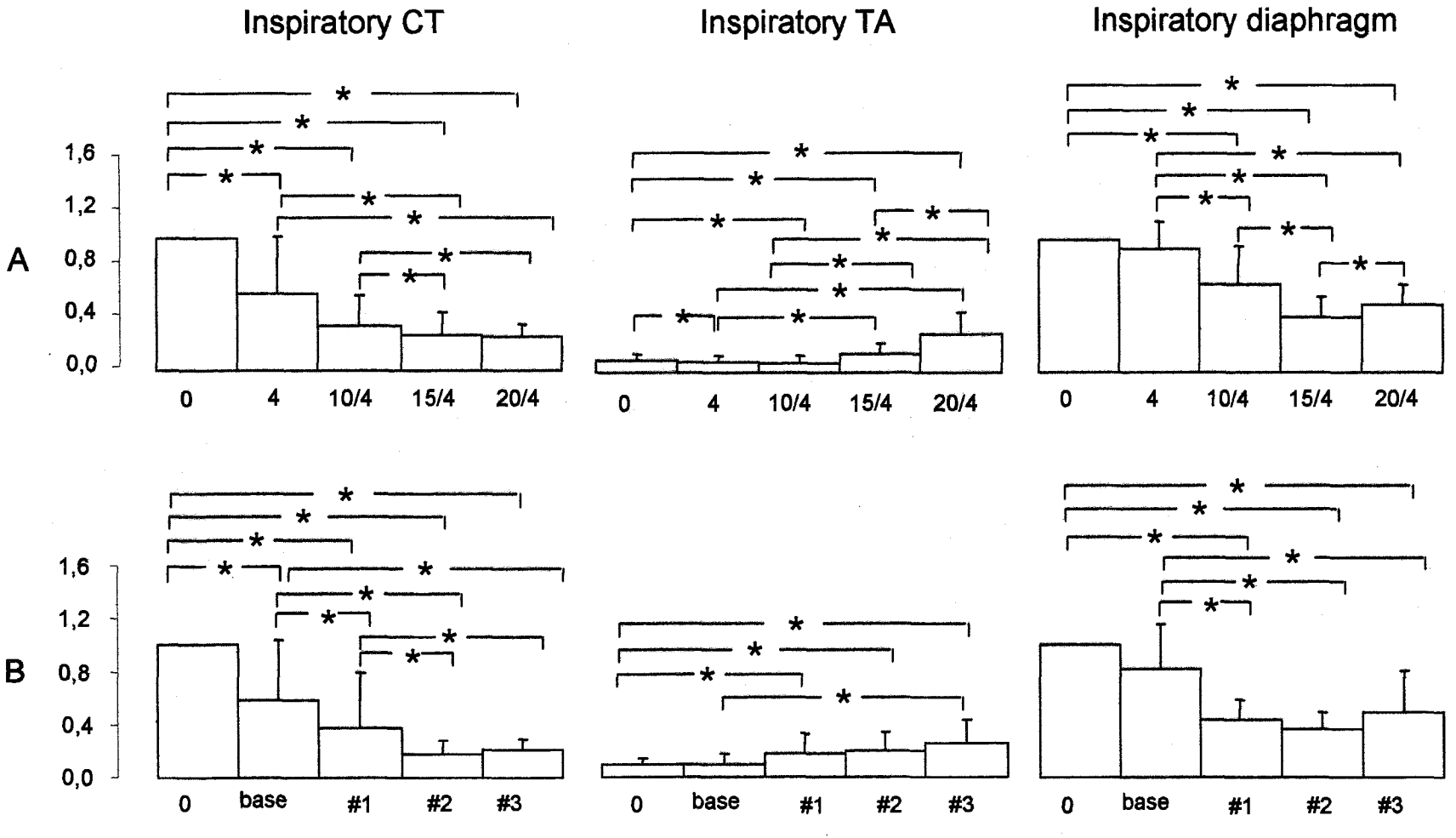

Inspiratory CT
Inspiratory TA
Inspiratory diaphragm
A
B
1,6
1,2
0,8
0,4
0,0
0
4
10/4
15/4
20/4
base
#1
#2
#3

Figure 3

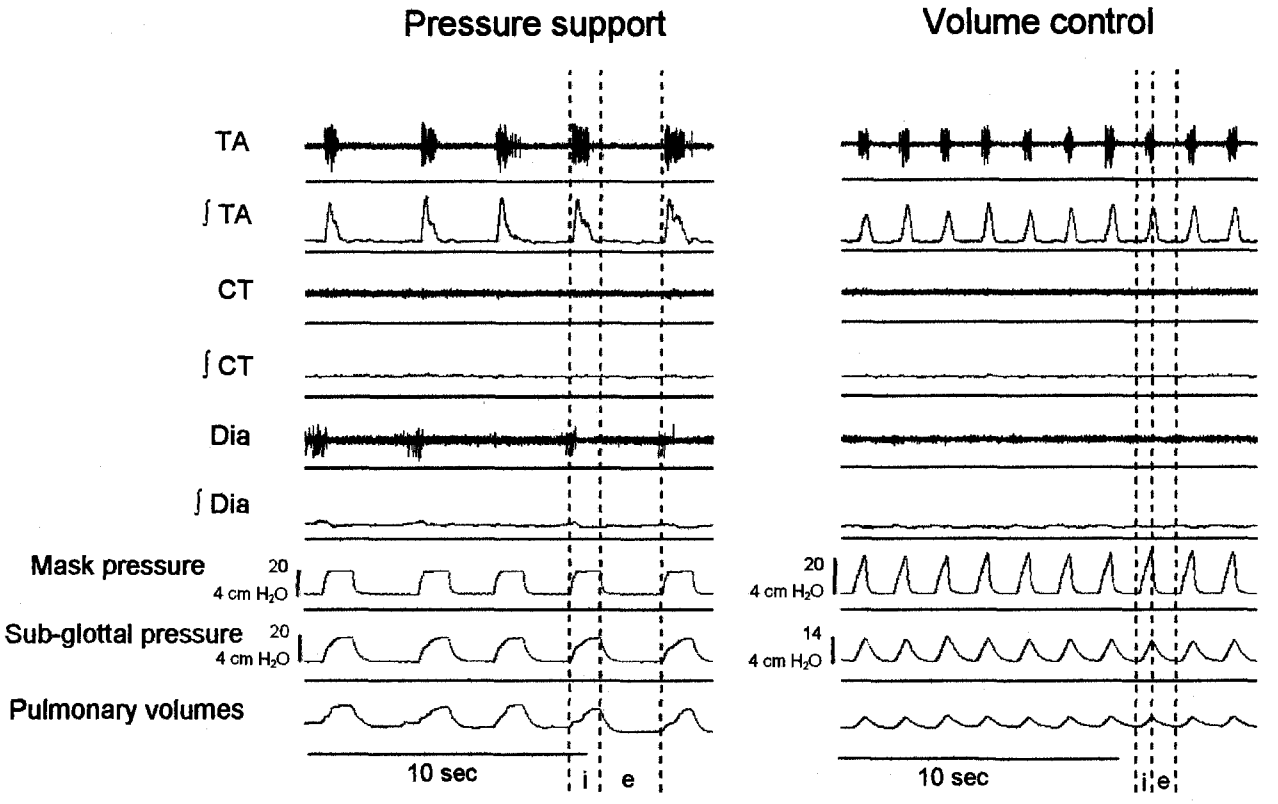

Pressure support
Volume control
TA
∫ TA
CT
∫ CT
Dia
∫ Dia
Mask pressure
20
4 cm H2O
Sub-glottal pressure
20
4 cm H2O
Pulmonary volumes
10 sec
i
e
20
4 cm H2O
14
4 cm H2O
10 sec
i
e

Figure 4

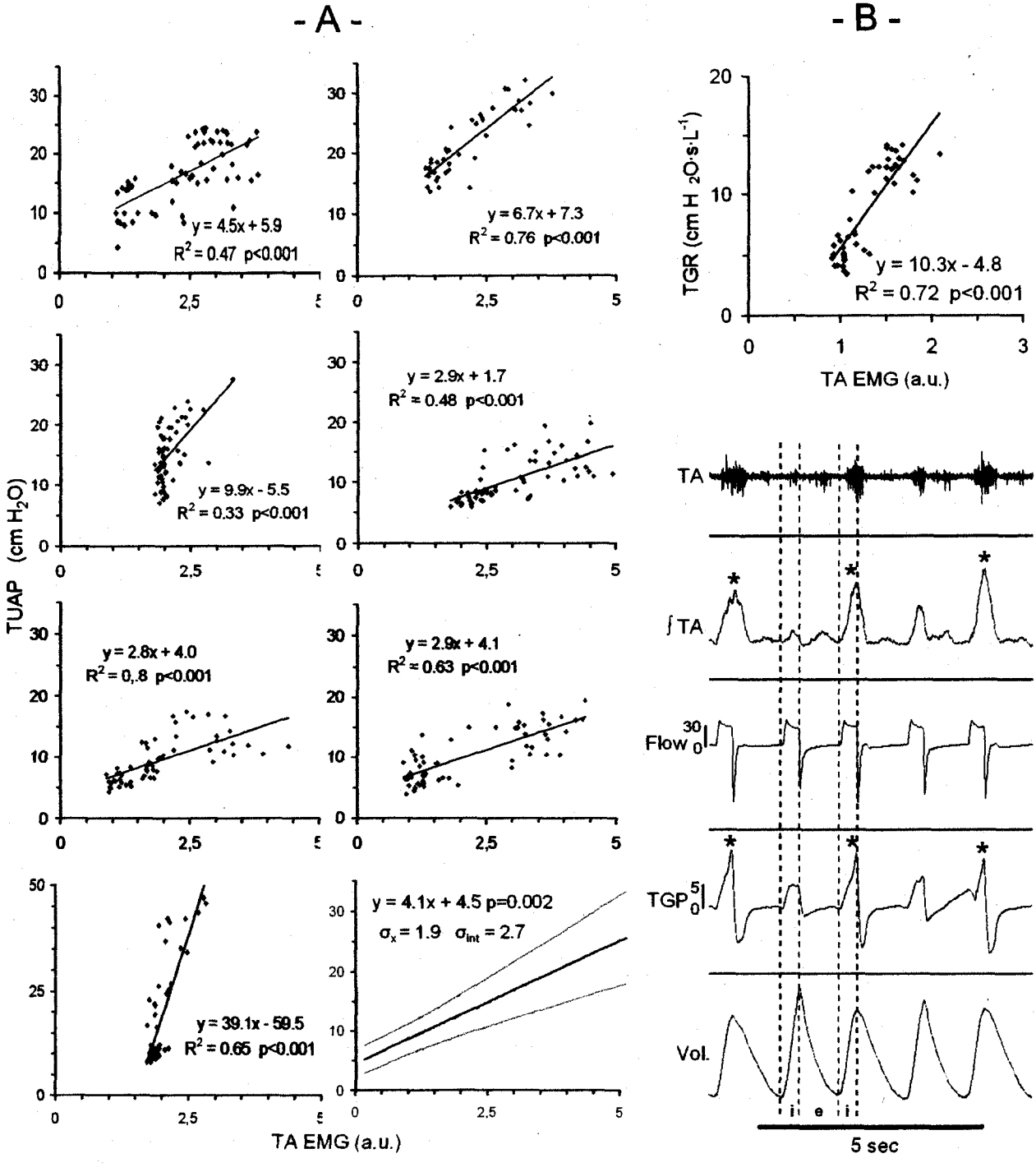
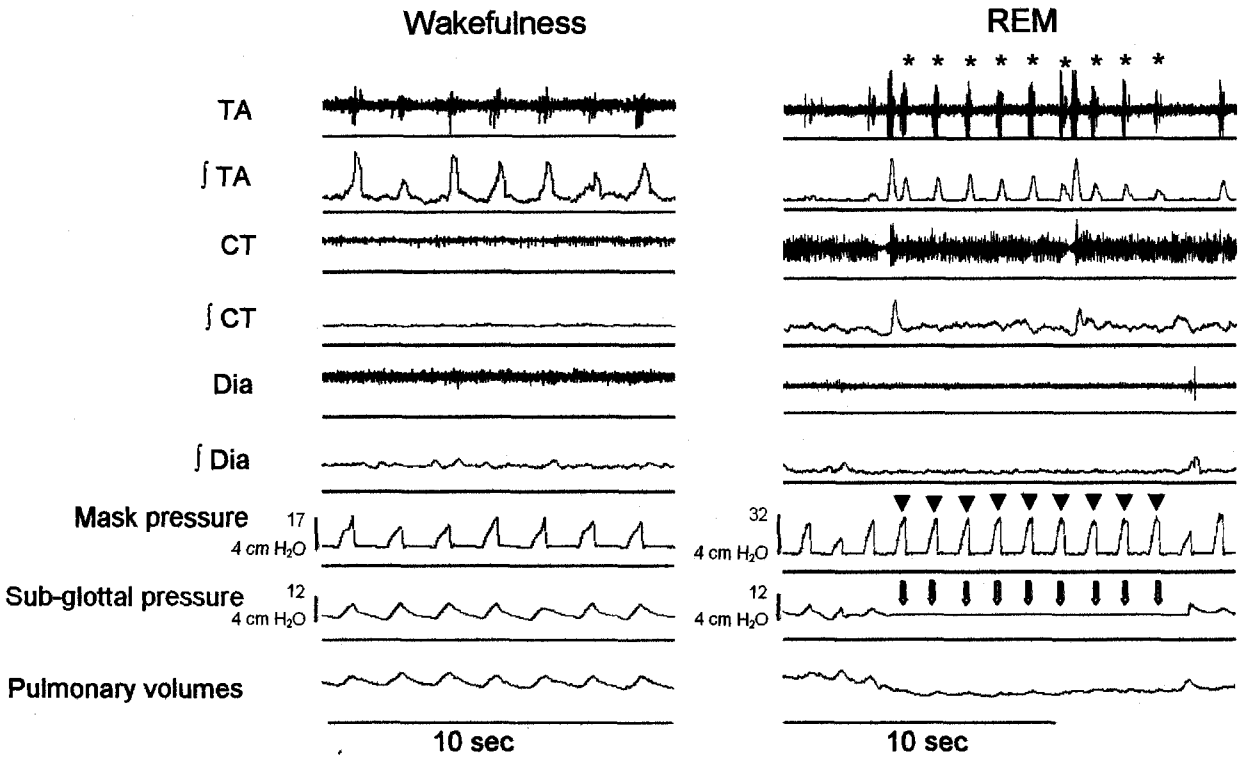

- A -
- B -
y = 4.5x + 5.9
R² = 0.47 p<0.001
y = 6.7x + 7.3
R² = 0.76 p<0.001
y = 9.9x - 5.5
R² = 0.33 p<0.001
y = 2.9x + 1.7
R² = 0.48 p<0.001
y = 2.8x + 4.0
R² = 0,.8 p<0.001
y = 2.9x + 4.1
R² = 0.63 p<0.001
y = 39.1x - 59.5
R² = 0.65 p<0.001
y = 4.1x + 4.5 p=0.002
σx = 1.9 σint = 2.7
TUAP (cm H2O)
TA EMG (a.u.)
TGR (cm H2O·s·L-1)
y = 10.3x - 4.8
R² = 0.72 p<0.001
TA EMG (a.u.)
TA
∫TA
Flow
TGP
Vol.
i e i
5 sec

Figure 5


Wakefulness
REM
TA
∫ TA
CT
∫ CT
Dia
∫ Dia
Mask pressure
17
4 cm H2O
32
4 cm H2O
Sub-glottal pressure
12
4 cm H2O
12
4 cm H2O
Pulmonary volumes
10 sec
10 sec

Discussion

Les résultats obtenus dans cette étude effectuée chez des agneaux nouveau-nés démontrent que la VPPIn entraîne à l'inspiration une diminution de l'activité des muscles dilatateurs glottiques (CT) et une augmentation des muscles constricteurs glottique (TA). De plus, nos résultats suggèrent que ces modifications de l'activité des muscles laryngés sont responsables d'une fermeture glottique active qui limite la ventilation pulmonaire en VPPIn. Ce sont donc les premières preuves directes que le rétrécissement glottique déjà observé chez les adultes par endoscopie lors de la VPPIn est causé par une modification de l'activité des muscles intrinsèques du larynx. De plus, cette étude nous offre pour la première fois des données sur l'impact de la VPPIn au niveau de la dynamique laryngée des nouveau-nés. Nous croyons que de tels résultats sont hautement pertinents pour l'étude de la physiologie respiratoire et pourraient être à l'origine de modifications significatives des traitements respiratoires en période néonatale.

Activité inspiratoire des muscles glottiques en nIPPV

Activité inspiratoire du muscle thyroaryténoïdien : Le muscle TA est bien établi comme un constricteur glottique expiratoire qui se contracte normalement au début de l'expiration (HARDING et al., 1986, KUNA et al., 1988, LU et al., 2005, LUDLOW, 2005, SAMSON et al., 2006, ZHOU et al., 1989). La contraction expiratoire du muscle TA est particulièrement importante en période néonatale comme mécanisme de freinage expiratoire, favorisant le maintien d'une capacité

résiduelle fonctionnelle (CRF) plus élevée. Les nouveau-nés ayant une cage thoracique moins rigide et un parenchyme pulmonaire moins compliant, ce maintien actif de la CRF prévient l'atélectasie pulmonaire et améliore l'oxygénation (BARTLETT, 1989, DIAZ et al., 1996, HARDING et al., 1986). Par ailleurs, la présence d'activité *inspiratoire* du TA est très rarement rapportée lors de la respiration normale chez un sujet sain (PRAUD et al., 1995). Une telle activité inspiratoire du muscle TA est cependant décrite dans différentes expériences ou dans des conditions pathologiques incluant : le gasping anoxique *in vivo* (HUTCHISON et al., 2002, THUOT et al., 2001) et *in vitro* (LIESKE et al., 2000); l'hypoxie ou l'anoxie (DUTSCHMANN et PATON, 2002); lors de l'injection intraveineuse de capsaïcine (LU et al., 2005); lors de l'occlusion des voies aériennes supérieures (KIANICKA et PRAUD, 1997); ou chez les patients souffrants de sclérose latérale amyotrophique (ISOZAKI et al., 1994). Les mécanismes physiologiques à l'origine de l'activité phasique inspiratoire du TA ainsi que les conséquences associées sont mal connus.

À notre connaissance, l'activation du muscle TA lors de l'inflation pulmonaire en VPPIn est une observation unique dont l'origine vient probablement de la stimulation des récepteurs des voies aériennes intra et/ou extra-thoraciques par l'augmentation de la pression transmurale. En effet, l'apparition plus précoce d'EMG du TA inspiratoire en mode pression de support (PC) qu'en mode volume contrôlé (VC) (voir figures 1 et 3 de l'article) pourrait être due à l'augmentation plus rapide et soudaine de la pression inspiratoire positive en mode PS. Premièrement, l'apparition inspiratoire dEMG du TA pourrait être stimulée par les

afférences des récepteurs broncho-pulmonaires intra-thoraciques. Une revue de littérature récente concernant l'impact des afférences pulmonaires sur la modulation des muscles des voies aériennes supérieures (BAILEY et FREGOSI, 2006) montre qu'une stimulation des récepteurs pulmonaires à adaptation lente inhibe l'activité du TA (BARTLETT et al., 1973, HARDING et al., 1986, HUANG et al., 1989). Par ailleurs, quelques données suggèrent que la stimulation des récepteurs pulmonaires à adaptation rapide et des fibres C pourraient augmenter l'activité phasique de l'EMG du TA (HOLMES et REMMERS, 1989, STRANSKY et al., 1973). Une augmentation des afférences vagales provenant de ces récepteurs pourrait donc expliquer les changements de l'activité inspiratoire du TA observés dans notre étude. Cependant, les changements de l'activité du TA cités dans ces études se retrouvaient tous dans la phase expiratoire du cycle respiratoire. Deuxièmement, il est aussi possible que l'apparition de TA inspiratoire soit stimulée par des afférences venant des barorécepteurs à pression positive situés dans les voies aériennes supérieures sur la muqueuse laryngée et pharyngée (MATHEW et al., 1984, SANT'AMBROGIO et al., 1983). En effet, une étude basée sur un modèle de larynx isolé chez le cochonnet a récemment démontré qu'une stimulation des barorécepteurs laryngés par une pression positive expiratoire entraîne une augmentation de l'activité EMG du muscle TA lors de l'expiration (STELLA et ENGLAND, 2001). Troisièmement, l'hypothèse que les récepteurs laryngés sensibles au débit (thermorécepteurs) (SANT'AMBROGIO et al., 1983, STELLA et ENGLAND, 2001) soient impliqués est peu probable car l'air provenant du ventilateur était réchauffé et humidifié dans notre protocole expérimental, empêchant de ce fait l'activation des

thermorécepteurs. Finalement, même si l'hypocapnie entraînée par une hyperventilation passive en VPPIn chez des adultes a déjà été reliée à une augmentation du TA expiratoire (KUNA et al., 1993), il est peu probable que ce soit le cas ici. En effet, la grande majorité des agneaux de notre expérience avaient des valeurs normocapniques durant tout le protocole. De plus, nous n'avons pas noté de différence dans l'EMG du TA entre les agneaux qui ont obtenu quelques valeurs hypocapniques et ceux dont les valeurs étaient normales.

Activité inspiratoire du muscle cricothyroïdien : Comme démontré récemment chez les humains et les agneaux, le muscle CT agit comme un dilatateur de la glotte lorsque associé au muscle cricoaryténoïdien postérieur lors de l'inspiration (KUNA et al., 1994, LUDLOW, 2005, SAMSON et al., 2006). Nos données démontrant la disparition de l'activité EMG inspiratoire du muscle CT sont en accord avec des observations similaires chez des humains adultes lors de VPPIn en mode PS (KUNA et al., 1993). La disparition concomitante de l'activité phasique du diaphragme et du CT est probablement en partie causée par l'augmentation des afférences vagales venant des récepteurs bronchopulmonaires à adaptation lente (BAILEY et FREGOSI, 2006). Deuxièmement, il est possible que la perte des pressions inspiratoires négatives soit la cause de la diminution de l'activité inspiratoire du CT. En effet, les pressions négatives inspiratoires en eupnée augmentent normalement l'activité du muscle cricoaryténoïdien postérieur (STELLA et ENGLAND, 2001). Finalement, bien que l'hypocapnie entraîne une diminution de l'activité

inspiratoire du CT (KUNA et al., 1993), ce mécanisme est peu probable dans notre étude comme nous l'avons précédemment expliqué pour le TA.

Fermeture glottique active lors de l'inspiration en VPPIn

L'augmentation de l'activité EMG du TA et la diminution de celle du CT lors de l'inflation pulmonaire suggère fortement que la glotte se referme de façon active en VPPIn, comme supposé par des observations endoscopiques en mode VC chez des adultes humains (RODENSTEIN, 2001). Cette équipe de chercheurs a émis l'hypothèse que la fermeture glottique inspiratoire qu'ils observent est très probablement secondaire à une activation des muscles laryngés adducteurs sans pour autant pouvoir le prouver expérimentalement. De notre côté, nous démontrons dans cette étude que l'augmentation de l'EMG du TA est fortement reliée à une augmentation de la pression à travers les voies aériennes (PTVAS) inspiratoire chez tous nos agneaux. Puisque ces mesures ont été effectuées dans un même mode ventilatoire pour chaque agneau (VC-3), nous pouvons affirmer que, à débit constant, l'augmentation des PTVAS indique une augmentation proportionnelle des résistances des voies aériennes supérieures. En somme, l'augmentation de l'EMG du TA est reliée avec une augmentation des résistances des voies aériennes supérieures. Cette augmentation des résistances pourrait théoriquement être reliée à une contraction des muscles constricteurs pharyngés ou encore à des mécanismes passifs comme un rétrécissement de l'ouverture laryngée causé par l'effet Venturi lors des hauts débits inspiratoires. Cependant, plusieurs résultats suggèrent fortement qu'une fermeture glottique active est au moins partiellement responsable de

l'augmentation des résistances des voies aériennes supérieures observée dans notre étude. Premièrement, nous avons montré dans l'article que l'augmentation du TA inspiratoire est fortement reliée à une augmentation des résistances au niveau des cordes vocales chez un agneau (figure 4B). Deuxièmement, les résultats obtenus chez des humains adultes démontrent que la glotte se rétrécit lors de l'inspiration en VPPIN en mode VC (JOUNIEAUX et al., 1995[1], JOUNIEAUX et al., 1995[2]). Finalement, l'arrêt complet de transmission des pressions du ventilateur au niveau trachéal démontré en sommeil agité suggère fortement un mécanisme actif (figure 5).

La conséquence principale d'une augmentation des résistances laryngées lors des inflations pulmonaires en VPPIn est de limiter la ventilation pulmonaire. Cela est évident sur l'iconographie en éveil de la figure 4B en éveil qui montre une diminution des volumes courants lorsque l'EMG du TA et les pressions trans-glottiques sont au plus haut. De plus, les bouffées d'activité du muscle TA observées en sommeil agité étaient assez importantes pour empêcher totalement la transmission des insufflations du ventilateur à la trachée (figure 5). Bien qu'une telle activité du muscle TA ait déjà été décrite chez des humains adultes en sommeil agité en eupnée (KUNA et al., 1988) et chez l'agneau nouveau-né en VPPIn (SAMSON et al., 2005), la relation avec la ventilation pulmonaire n'a pas été discutée. Finalement, une autre conséquence d'une augmentation des résistances laryngées est d'augmenter le risque de distension gastro-intestinale et de perforation gastrique si les pressions des voies aériennes supérieures

dépassent la pression de fermeture du sphincter œsophagien inférieur (GARLAND et al., 1985).

Bien que notre protocole ne permette pas de comparer directement les modes PS et VC en ce qui concerne les résistances glottiques lors des inflations pulmonaires, nous avons noté quelques différences qui méritent mention. Premièrement, comme décrit dans l'article, l'EMG du TA en mode PS chez tous nos agneaux était maximal en début d'inspiration et diminuait progressivement à zéro avant la fin de l'inspiration, permettant une transmission des pressions du ventilateur à travers une glotte plus ouverte (voir figure 1). De l'autre côté, le mode VC était associé avec une augmentation des pressions et de l'activité du muscle TA tout au long de l'inspiration jusqu'à un pic à la fin de celle-ci (figure 3). Ceci suggère que, en mode VC, les résistances glottiques sont maximales alors que les pressions des voies aériennes supérieures sont à leur plus haut niveau limitant ainsi la ventilation pulmonaire. De plus, la transmission des pressions à travers la glotte en mode VC devait s'effectuer à l'intérieur d'un temps inspiratoire plus court. Ces observations pourraient d'ailleurs expliquer que les PTVAS soient beaucoup plus élevées en mode VC que PS (17,5 et 2,3 cm H_2O respectivement, voir tableau 1). Bien que suggérant que le mode PS est plus efficace que le mode VC pour transmettre les pressions inspiratoires du ventilateur dans les voies aériennes inférieures, nous ne pouvons pas confirmer une telle hypothèse avec cette étude.

Pertinence clinique

Les résultats publiés dans ce mémoire proviennent d'une étude expérimentale physiologique ayant un intérêt clinique. Le choix du modèle expérimental étudié, l'agneau nouveau-né, nous a permis de démontrer pour la première fois que la VPPIn entraîne une fermeture laryngée active. Cependant, ce modèle animal comporte évidemment des caractéristiques limitant l'extrapolation des résultats à l'humain. En effet, bien que des nouveau-nés à terme soient fréquemment ventilés en VPPIn en néonatologie, la plupart des patients nécessitants de tels soins sont des prématurés. De plus, alors que les pressions inspiratoires utilisées représentent bien la clinique humaine (10 à 20 cm H_20), les volumes courants utilisés en VC (maximum de 23 ml/kg en moyenne dans VC-3) paraissent supra-physiologiques. Rappelons cependant que les gaz artériels ont démontrés que nos agneaux sont restés normocapniques même lors de la ventilation maximale (VC-3). Il est donc peu probable qu'ils aient été hyperventilés de façon importante malgré des volumes courants élevés. De plus, bien que les volumes courants normaux pour les agneaux nouveau-nés ne soient pas connus dans la littérature, notons que les paramètres ventilatoires nécessaires pour garder nos agneaux normocapniques en chirurgie se retrouvent fréquemment entre 15 et 25 ml/kg avec une fréquence de 40 à 60 respirations par minute. Il est donc probable que les volumes courants chez les agneaux nouveau-nés soient plus importants que les nouveau-nés humains ayant un âge et un poids comparables. Bref, bien que l'intérêt clinique de tels résultats soit évident, nous ne pouvons conclure avec certitude que ces phénomènes se produisent aussi chez les nouveau-nés humains.

Perspectives

Les résultats des travaux effectués lors de ce projet de maîtrise posent de nouvelles questions auxquelles le Laboratoire de recherche respiratoire néonatale tentera de réponde dans les prochaines années. Premièrement, le laboratoire a déjà conçu un nouveau modèle d'isolation des voies aériennes supérieures ainsi que d'ablation des afférences pulmonaires vagales par section du nerf vague à l'aide de la vidéothoracoscopie. En vérifiant respectivement la contribution des mécanorécepteurs laryngés et des afférences broncho-pulmonaires, ces deux modèles permettront de préciser quels sont les mécanismes physiologiques responsables des changements notés dans la dynamique des muscles laryngés lors de la VPPIn. Deuxièmement, un projet de collaboration avec une équipe travaillant sur un nouveau mode de ventilation assistée ajustée par les afférences neurologiques diaphragmatiques (NAVA, *neurally adjusted ventilatory assist)* est en cours afin de déterminer si ce dernier entraînera aussi une fermeture glottique active. Finalement, il serait intéressant de vérifier l'impact de la prématurité sur les réponses laryngées à la VPPIn à l'aide d'un modèle d'agneau prématuré afin de se rapprocher encore plus des situations cliniques rencontrées chez l'humain.

Conclusion

Cette étude démontre que la VPPIn en mode PC ou VC entraîne à l'inspiration une fermeture glottique active secondaire à une augmentation de l'activité des muscles constricteurs (TA) et une diminution des muscles dilatateurs (CT) de la glotte chez les agneaux nouveau-nés. Cette fermeture glottique entraîne une augmentation des résistances laryngées qui limitent significativement la ventilation pulmonaire, tout particulièrement en mode VC.

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